

Knowledge and Awareness about the teratogenic effects of oral Isotretinoin among women in Saudi Arabia

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ABSTRACT

Background: Isotretinoin, commonly known as 13-cis retinoic acid, is the most effective medication for treating acne. This drug's adverse effects include dry skin and mucous membranes, an elevated lipid profile and regular muscle aches.

This study aimed to assess the knowledge and awareness about the teratogenic effects of using oral isotretinoin among childbearing-age women in Saudi Arabia. **Methodology:** This is an observational cross-sectional study that was conducted between February 2022 to November 2022 in Saudi Arabia. A questionnaire was distributed online and women of childbearing age will fill it out and the sample size was estimated by using the Qualtrics calculator with a confidence level of 95% and a sample size of 384. Statistical analysis was conducted with aid of Statistical package for social sciences.

Results: The study included 1680 female participants, 51% of study participants aged between 20 - 31 years old. 85.1% heard about isotretinoin. 71.5% know side effects of isotretinoin. Isotretinoin is currently used by 14.6% of participants. Isotretinoin was used by 7.8% of women after marriage. Contraception is recommended for 8.8% of those on Isotretinoin. In the case of a pregnancy while using Isotretinoin, 12.4% of participants were advised about the possibility of fetal congenital abnormalities. After the therapy period, 3.3% of women had a pregnancy test. **Conclusion:** Despite to the report's results, women of reproductive age are frequently unaware of isotretinoin's adverse effects.

Keywords: Isotretinoin, Teratogenicity, Knowledge, Awareness, Side effects, Saudi Arabia.

1. INTRODUCTION

A synthetic medicine called isotretinoin, also referred to as 13-cis retinoic acid, is the most effective for treating acne (Forbat et al., 2018), is primarily used to treat sebaceous gland pathology but is also can use to treat a variety of dermatological conditions, including, rosacea, scarring alopecia and non-

melanoma skin cancer prevention (Draghici et al., 2021). Dry skin and mucous membranes, an increased lipid profile and frequent muscle aches have been mentioned as side effects of this drug. It is also generally known to be teratogenic (Al-Mekhlafi et al., 2021).

The American-Academy-of-Dermatology (AAD) suggests administering isotretinoin. For moderate to severe acne that does not respond to other treatments, isotretinoin, which is a vitamin A derivative that received its initial approval in the U. S. in 1982 is used to treat severe acne (Younis & Al-Harbi, 2019). Used for the treatment of severe or moderate acne that does not respond to other drugs, isotretinoin is approved as the first-line therapy (Jarab et al., 2022). Acne can affect anyone in any age group, but it is most common in teenagers. It affects between 80% and 90% of all teenagers, making it the most prevalent skin condition worldwide (Saeed et al., 2021). The FDA received reports from 1997 through 2017 about of 6740 pregnancies with women taking isotretinoin, with a spike in 2006 (768 pregnancies) before settling into a range of 218 to 310 yearly reports of pregnancies after 2011 (Tkachenko et al., 2019).

A study by (Molla et al., 2020) reported that more than 60% of the participants among Al-Madinah population knew about isotretinoin side effects and 54.4% had been notified about them (Saeed et al., 2021; Molla et al., 2020). Another study published in 2019, in Saudi Arabia reveals that 88.9% of Al-Ahsa population participants know that isotretinoin is inappropriate for use in pregnant women due to its teratogenic effects, Additionally, 58.7%, 44.1% and 53.3% of participants correctly identified lipid profile disturbance, liver dysfunction and depression as side effects respectively (Albadr et al., 2019; Tkachenko et al., 2019). Another study done by (Murad et al., 2020) among female students at Taibah University, dryness was the most widely known adverse effect, with 65.3% of participants reporting it, followed by hepatic side effects 50% and teratogenicity 37.3%. Up to our knowledge, there's scanty data on awareness about the teratogenic effects of using oral isotretinoin in Saudi Arabia. Hence, the purpose of this study is to evaluate females' knowledge and awareness about the teratogenic effects of using oral isotretinoin in Saudi Arabia.

2. MATERIALS AND METHODS

Study design

This is an observational cross-sectional study that was conducted between February 2022 to November 2022 in Saudi Arabia.

Study setting

Participants, recruitment and sampling procedure: The questionnaire was distributed online and women of childbearing age fell it out.

Inclusion and Exclusion criteria

In this study, we included all women of childbearing age living in Saudi Arabia who have agreed to participate in our study. We excluded males and people who are not within our age limit.

Sample size

The sample size was estimated by using the Qualtrics calculator with a confidence level of 95% and a sample size of 385.

The Sample size was estimated using the formula: $n = P(1-P) * Z\alpha^2 / d^2$ with a confidence level of 95%;

n: Calculated sample size

Z: The z-value for the selected level of confidence (1- a) = 1.96.

P: An estimated prevalence of knowledge

Q: $(1 - 0.50) = 50\%$, i.e., 0.50

D: The maximum acceptable error = 0.05.

So, the calculated minimum sample size was:

$$n = (1.96)^2 * 0.50 * 0.50 / (0.05)^2 = 384.$$

Method for data collection and instrument (Data collection Technique and tools)

The questionnaire was obtained with the permission of Dr. Kholoud Mohammed A Bakheet (Bakheet et al., 2020) and Dr. Mana Alharbi (Alharbi, 2020) and we used it as our tool. The questionnaire includes three parts first, demographic that's including gender, age, nationality and marital status, educational level, the Second part consists of 5 items regarding knowledge and awareness of the side effects of isotretinoin among women, We have taken into consideration of scoring system as the correct

answers get 20 points among Knowledge, Wherefore, we consider having 40 points (i.e., < 50%) is a poor knowledge while a score of 60 is fair knowledge and those who gets 80 or more (i.e., > 75%) considered to have good knowledge and the third part about awareness that focused on Married women and their awareness about using isotretinoin and it's teratogenic impacts, having 44 points (i.e., < 50%) is a poor awareness while having 66 and more (i.e., > 75%) considered to have good awareness and having between 45-65 is considered fair awareness about the usage and drug teratogenicity.

Pilot test

The questionnaire was distributed on above 15 individuals and asked to fill it. This was done to measure the understanding of the questionnaire and the feasibility of the study. The final data of the study doesn't include the pilot data of the study.

Analyzes and entry method

Statistical analysis was conducted with aid of Statistical package for social sciences (IBM®SPSS®) version 24, after inserting the data into a Microsoft excel spreadsheet. Descriptive statistics (i.e., frequency, percentage, mean and standard deviation) was calculated. P-values less than 0.05 will be considered statistically significant.

3. RESULTS

The study included 1680 female participants, 51% of study participants aged between 20 - 31 years old and 17.5% aged between 31-40 years old. 95.1% of participants were Saudi. 44.7% were married. 74.2% had university education as illustrated in table (1).

Table 1 Sociodemographic characteristics of participants (n=1680)

Parameter	No.	Percent
Age	Less than 20	236
	20 – 30	856
	31- 40	294
	41 – 50	200
	51- 60	85
	More than 60	9
Nationality	Saudi	1598
	Non-Saudi	82
Region	Courtyard	118
	hollow	8
	Northern borders	3
	Riyadh	153
	Al-Qassim	205
	Medina	123
	Eastern Province	305
	Tabuk	51
	Jazan	192
	hail	9
	difficult	190
	Mecca	246
	Najran	77
Marital status	single	855
	married	751
	divorced / widow	74
Education level	illiterate	4
	Primary	14
	intermediate	31
	secondary	307

	university	1247	74.2
	Master's/PhD	77	4.6

Table 2 shows that, 85.1% heard about isotretinoin. 71.5% know side effects of isotretinoin (68% defined dehydration, 54.8% defined congenital anomalies of fetus, 27% reported increased fats in blood and 35.7% depression). 68.6% of participants have worries when thinking about starting Isotretinoin (Figure 1).

Table 2 Knowledge of participants of Isotretinoin (n=1680)

Parameter		No.	%
Heard of Isotretinoin / Roctan	Yes	1429	85.1
	No	251	14.9
Know the side effects of this drug	Yes	1202	71.5
	No	478	28.5
Side effects that you know about this drug	Dehydration	1143	68.0
	Congenital anomalies of the fetus	921	54.8
	An increase in the level of fats in the blood	453	27.0
	Constipation	303	18.0
	Depression	600	35.7
	I don't know	366	21.8
Worries when thinking about starting Isotretinoin / Roaccutane	General side effects	1153	68.6
	Congenital malformations of the fetus	253	15.1
	The duration of treatment	274	16.3

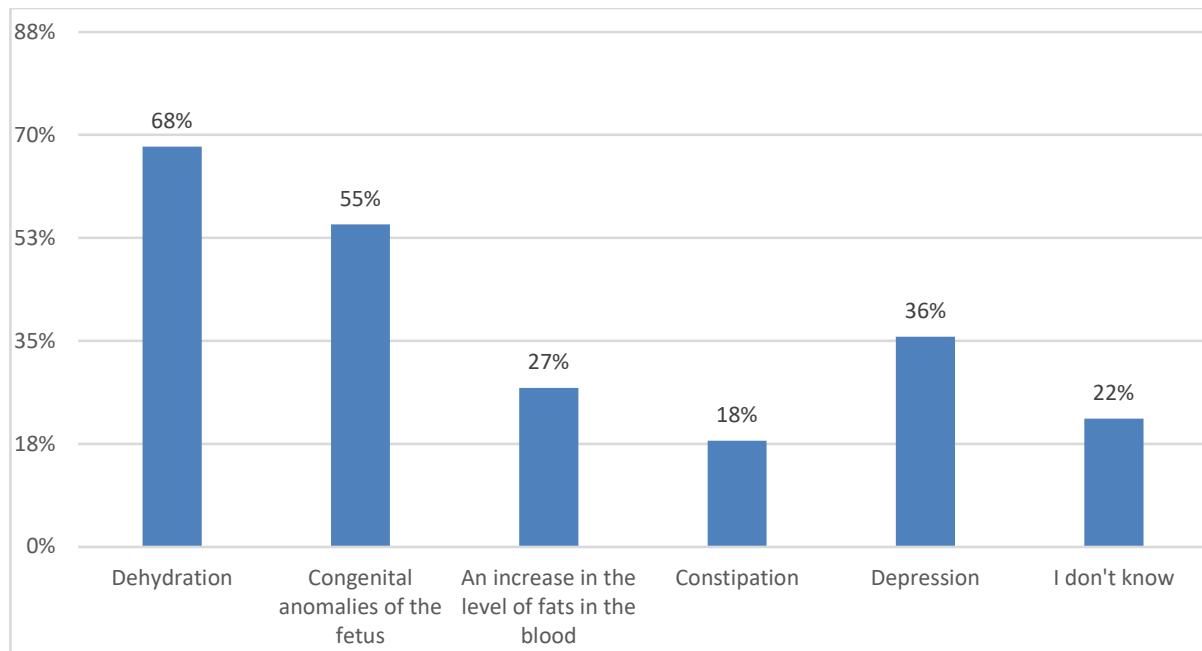


Figure 1 Knowledge of participants of Side effects that you know about Isotretinoin drug (n=1680)

In table 3, 14.6% of participants currently use Isotretinoin. 7.8% used Isotretinoin after marriage. 8.8% were advised to use contraceptives while you are using Isotretinoin (10% of them were advised by doctor). 12.4% of participants were informed of possible congenital malformations of the fetus in the event of a pregnancy while using Isotretinoin (8.7% of them were informed by doctor).

Table 3 Participants' use of Isotretinoin (n=1680)

Parameter		No.	%
Currently using Isotretinoin / Roaccutane	Yes	246	14.6
	No	1434	85.4
Used Isotretinoin / Roaccutane after marriage	Yes	131	7.8
	No	734	43.7
	I'm a single girl	815	48.5
Advised to use contraceptives while you are using Isotretinoin / Roaccutane	yes	148	8.8
	no	222	13.2
	I did not use Isotretinoin / Roaccutane after marriage	495	29.5
	I'm a single girl	815	48.5
If yes to, methods of contraception been advised to use	two ways	89	5.3
	More than two methods	49	2.9
	I was not informed of the need to use contraceptives during treatment	64	3.8
	I did not use Isotretinoin / Roaccutane after marriage	663	39.5
	I'm a single girl	815	48.5
Who advised you to use contraceptives	A pharmacist	20	1.2
	the doctor	168	10.0
	No one told me	43	2.6
	I prescribed it to myself	58	3.5
	I did not use Isotretinoin / Roaccutane after marriage	576	34.3
	I'm a single girl	815	48.5
Informed of possible congenital malformations of the fetus in the event of a pregnancy while using Isotretinoin / Roaccutane	yes	208	12.4
	no	125	7.4
	Have not used Isotretinoin / Roaccutane after marriage	532	31.7
	I'm a single girl	815	48.5
If yes, who informed	the doctor	146	8.7
	I read about it myself	82	4.9
	No one informed me/ I didn't know	56	3.3
	I have not used Isotretinoin / Roaccutane after marriage	581	34.6
	I'm a single girl	815	48.5

In figure (2), 14.6% of participants currently use Isotretinoin / Roctan and 84.4% of participants currently not used it.

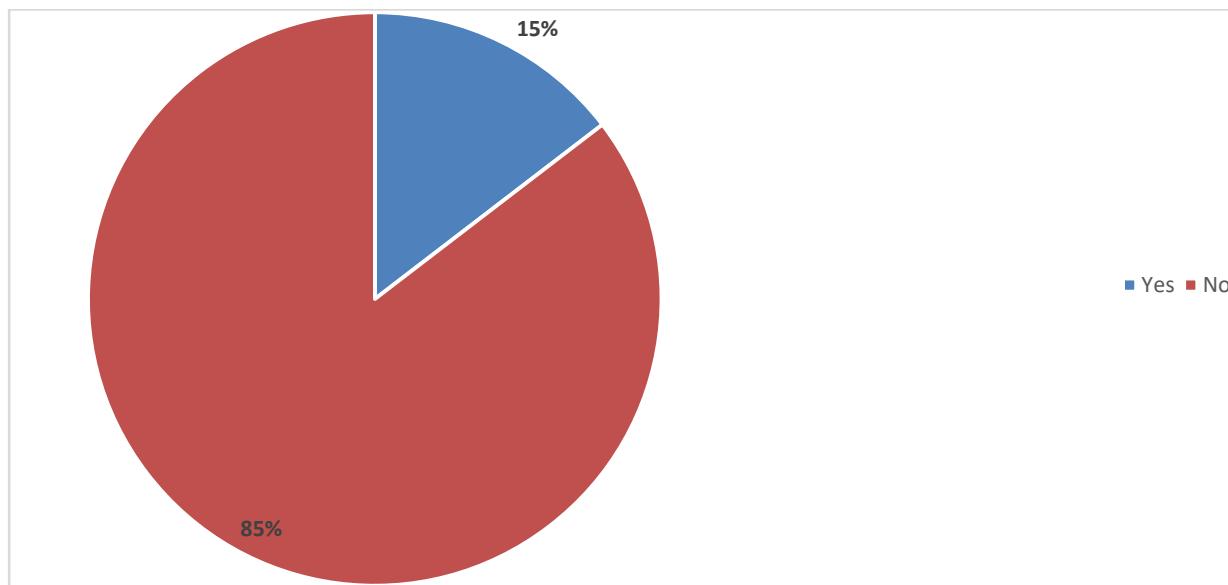


Figure 2 Participants use of Isotretinoin / Roctan (n=1680)

As illustrated in table (4), 3.3% had pregnancy test after treatment period, 2.9% during treatment period and 5.3% before treatment period. 1.1% of studied sample got pregnant during the first month after stopping treatment while 2.1% got pregnant a month before starting treatment.

Table 4 Attitude of participants towards Isotretinoin (n=1680)

Parameter		No.	%
Had a pregnancy test (before, during or after) use of Isotretinoin / Roctan	After the treatment period	55	3.3
	During the treatment period	49	2.9
	before the treatment period	89	5.3
	I did not use Roaccutane after marriage	672	40.0
	I'm a single girl	815	48.5
Get pregnant during (a month before starting the treatment, during the treatment period, or within a month after stopping the treatment)	No, I did not get pregnant	167	9.9
	Yes, during the first month after stopping treatment	19	1.1
	Yes, a month before starting treatment	36	2.1
	Did not use Roaccutane after marriage	643	38.3
	I'm a single girl	815	48.5
If got pregnant, informed doctor	Yes	46	2.7
	No, I did not get pregnant	110	6.5
	No, I did not inform the doctor about the pregnancy	40	2.4
	I have not used Isotretinoin / Roaccutane after marriage	669	39.8
	I'm a single girl	815	48.5

Table 5 Knowledge of participants of Isotretinoin in association with sociodemographic characters of participants (n=1680)

		Knowledge of Isotretinoin / Roctan		Total (N=1680)	P value
		Yes	No		
Age	Less than 20	197	39	236	0.001
		13.8%	15.5%	14.0%	
	20 - 30	775	81	856	
		54.2%	32.3%	51.0%	
	31- 40	239	55	294	
		16.7%	21.9%	17.5%	
	41 - 50	150	50	200	
		10.5%	19.9%	11.9%	
	51- 60	61	24	85	
		4.3%	9.6%	5.1%	
	More than 60	7	2	9	
		0.5%	0.8%	0.5%	
Nationality	Saudi	1358	240	1598	0.691
		95.0%	95.6%	95.1%	
	Non-Saudi	71	11	82	
		5.0%	4.4%	4.9%	
Marital status	single	757	98	855	0.001
		53.0%	39.0%	50.9%	
	married	612	139	751	
		42.8%	55.4%	44.7%	
	divorced / widow	60	14	74	
		4.2%	5.6%	4.4%	
Education level	illiterate	1	3	4	0.001
		0.1%	1.2%	0.2%	
	Primary	5	9	14	
		0.3%	3.6%	0.8%	
	intermediate	21	10	31	
		1.5%	4.0%	1.8%	
	secondary	240	67	307	
		16.8%	26.7%	18.3%	
	university	1091	156	1247	
		76.3%	62.2%	74.2%	
	Master's/PhD	71	6	77	
		5.0%	2.4%	4.6%	

4. DISCUSSION

Due to its potent sebum-suppressive effects, which are predominantly brought on by sebocyte death, isotretinoin is regarded as the most effective medication for the treatment of severe types of acne vulgaris. Since the drug's introduction to the market in 1982, the teratogenic effects caused by isotretinoin have been documented (Alharbi, 2020). In Saudi Arabia, issues about isotretinoin have already been looked into. The public's knowledge of the use and safety of goods containing isotretinoin was investigated in a study. The study discovered that although a significant portion of participants were aware of the drug's teratogenicity, some women were unaware that they needed to cease using it before becoming pregnant (Younis & Al-Harbi, 2019).

According to another Saudi study, the vast majority (91%) of participants reported to be aware of and comprehend the negative effects of using isotretinoin, which is consistent with earlier-research (Al-Mekhlafi et al., 2021). While they indicated that 77% of study participants are educated about the medicine and its purposes, reported that 62 of their respondents are generally aware of

the negative effects (Alharbi, 2020; Molla et al., 2020). Around 85% of the sample population in different research of Saudi women in Western Saudi Arabia was found to be aware of the medication's negative effects (Sa et al., 2020). The fact that a sizeable fraction (29%) of these "knowledgeable" women in this survey acquire their information from places like the Internet, pamphlets and friends and family raises some red flags because all of these sources run the risk of providing inaccurate information or misrepresenting something.

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The results of other investigations on the use of isotretinoin-during-pregnancy in other Western nations were comparable, proving that the Netherlands is not the only country with low PPP compliance (Autret-leca et al., 2010; Kass et al., 2008; Venereol, 2005). The most recent isotretinoin PPP in the USA, known as iPLEDGE, has been in place since 2006 and is more stringent than the EU PPP. All stakeholders must register with the internet-based iPLEDGE system, which involves monthly reporting on prescriptions, pregnancy testing, contraceptive use and risk acknowledgment (Kass et al., 2008). When compared to the previous PPP known as SMART (System to Manage Accutane-Related Teratogenicity), the predicted pregnancy rate among isotretinoin users in the USA with the iPLEDGE PPP was 2.7/1000 treatment courses and only marginal gains in contraceptive measure adherence were seen (Abroms et al., 2006; Kass et al., 2008).

5. CONCLUSION

According to the study's findings, women of reproductive age are often unaware of isotretinoin's negative effects, notably its potential for teratogenicity. These findings imply that in order to enhance both doctor and patient compliance, substantial steps and changes must be made. Additionally, it is advised that the doctor-patient relationship be open and reassuring to women and that communication be thorough.

Recommendations

We recommend that further educational campaigns should be inaugurated to raise Awareness and knowledge about teratogenic effects of oral Isotretinoin among women in Saudi Arabia.

Ethical approval

The research proposal was approved by the Regional Research and Ethics committee of ministry of health in Jeddah with letter number (A01563).

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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